STIC-ILL

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1. PNAS, 1997, 94(8):4000-4004
2. Cancer Research, 1992 Jan 1, 52(1):127-131
3. Expert Opinion on Investigational Drugs, 1997, 6(2):169-172
4. Antibody Immunoconjugates and Radiopharmaceuticals, 1993, 6(1):69

12830288

24

INTERNALIZATION AND INTRANUCLEAR INTERACTION OF ANTI-CANCER MONOCLONAL ANTIBODIES.

E.M. RAKOWICZ-SZULCZYNSKA, D.G. MCINTOSH, & M.L. SMITH
University of Nebraska Medical Center, Department of Obstetrics and Gynecology, 600 South 42nd Street, Omaha, Nebraska 68198-3255.

We have found that some monoclonal antibodies (MAb) directed against tumor cells, after binding to the cell surface antigens, are internalized into the cytoplasm and rapidly translocated to the nucleus. Nuclear accumulation of different MAbs was tested by fractionation of cells exposed to ^{125}I-MAb, or by indirect immunofluorescence staining. Inside the nucleus, intact ^{125}I-MAb-molecules bind to specific chromatin antigens which usually exhibit different molecular weights than the cell surface antigens. MAbs against cell surface antigens immunoprecipitate the chromatin antigens and recognize these antigens in Western blotting, which suggests that both the cell surface and nuclear antigens express the same epitopes. The reaction of internalization is highly specific and usually only one from few MAbs obtained against the given antigen is internalized and translocated to the cell nucleus. Internalization does not correlate with the growth factor receptor-structure of the cell surface antigens. For example, MAbs ME 82.11 or ME 20.4, both against NGF receptor are not internalized, while the original ligand (NGF) penetrates the cell very efficiently and binds to the chromatin antigen. EGF receptor mediates effectively internalization of both EGF and MAb 425 against the protein domain of the receptor, but not of MAb Br 15-6A against the carbohydrate Y determinant attached to that receptor. Instead, MAb Br 15-6A is internalized by cells that express Y determinant attached to a protein of the Mr 92,000 in breast carcinomas and 108,000 Mr in colorectal carcinomas. It is noteworthy that another MAb against Y determinate, MAb Br 55.2, which binds to the same antigens as MAb Br 15-6A, is never internalized. The number of MAb-molecules which are translocated to the nucleus is specific for the given cell lines and the specific MAb, and varies from 1000 molecules to a hundred thousand molecules. MAb ME 491 against a melanoma-associated antigen accumulates in the chromatin at the level of 1000-10,000 molecules per nucleus and inhibits rRNA synthesis by 70%. In contrast, nuclear accumulation of MAb against the 88 KDa antigen expressed on breast carcinoma cells exceeds 100,000 molecules/nucleus, which does not affect RNA synthesis. However, when MAb against the 88 KDa antigen is labeled with ^{125}I, it induces an almost complete fragmentation of the chromatin (DNA). Nuclear accumulation of nondegraded MAb directed against the cell surface antigens indicates that MAb may be potentially used to inhibit directly specific genes. Alternatively, MAb able to penetrate the cell nucleus might be used as vehicles for radioactive ligands as well as for toxins or inhibitors of replication or transcription. We suggest that in addition to the therapeutic value, MAb which are internalized and translocated to the nucleus may shed some light on the conservative function of some cell surface antigens (epitopes).

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• Immunotherapy of Multiple Drug Resistant Tumors with Anti-P-Glycoprotein Monoclonal Antibodies. L. Rittmann-Grauer, E. Bischoff, M. Yong, and D. Mackensen. Hybritech Incorporated, San Diego, Ca. 92121

Acquired drug resistance is a central problem in clinical cancer chemotherapy. Multiple drug resistance (MDR) has been strongly linked to the overexpression of a membrane associated molecule, p-glycoprotein which appears to play a role in drug efflux. Monoclonal antibodies (mabs) which recognize the extracellular portion of p-glycoprotein were evaluated for their ability to inhibit the growth of multiple drug resistant tumors in nude mice.

Mice were innoculated s.c with the human mdr ovarian carcinoma line, $2780^{AD}10$. On days 2 and 7 mice received 100ug of anti-p-glycoprotein mab, HYB162. Control mice (10/10) developed tumors and died by day 45. In contrast, the antibody treated mice 10/10 remained tumor free for the duration of the experiment (210 days). Comparable treatment of the parental, drug sensitive tumor, A2780 failed to produce inhibition of growth suggesting that the effect was dependent on the presence of the drug resistance marker.

This antigen/antibody system is particularly attractive for immunotherapy because it lacks several of the characteristics which have led to failure of immunotherapy in the past. For example, 1) there is no evidence that this antigen is shed or found in the serum of drug resistant patients, 2) the antigen is not immunologically modulated and, 3) the location of antigen on the luminal surfaces of normal secretory tissues may not be accessible to the antibody.

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• AN IMMUNOTOXIN, AN ANTIBODY-DRUG CONJUGATE AND A HETERODIMERIC ANTIBODY CONJUGATE SHOW TUMOR SPECIFIC EFFICACY IN ANIMAL SURVIVAL MODELS. Sudhir A. Shah, Cynthia A. Ferris, Susan M. Derr, Lizabeth A. Bourret, Ravi V. J. Chari, Yeldur P. Venkatesh, Victor S. Goldmacher, John M. Lambert and Walter A. Blattler. ImmunoGen Inc., 148 Sidney Street., Cambridge, MA 02139.

The therapeutic efficacies of an immunotoxin, an antibody-drug conjugate and a heterodimeric antibody conjugate (with activated human PBL's) were assessed in xenograft mouse tumor models. Anti-CD19 monoclonal antibody, anti-B4, conjugated to blocked ricin (Anti-B4-bR, 50 or 75 ug/kg/d, i.v. x 5) was evaluated in SCID mice bearing 7 d established human B-cell lymphoma ($4x10^6$ Namalwa cells, i.v.). Controls included treatment with unconjugated anti-B4 antibody (2 mg/kg/d, i.v. x 5) or a non-specific antibody-blocked ricin conjugate (N901-bR, 100 ug/kg/d, i.v. x 5). Anti-transferrin receptor antibody, 5E9, conjugated to a maytansinoid (5E9-Maytansinoid, 7 mg/kg/d, on days 1, 3, 5) was injected i.v. in SCID mice one hour after i.p. injection of A375 human melanoma cells ($3.5x10^7$). Three i.v. injections of a mixture of unconjugated 5E9 antibody (15 mg/kg/d x 3) plus free maytansinoid drug (0.11 mg/kg/d x 3) served as a control. The anti-tumor efficacy of a heterodimeric conjugate, anti-B4-anti-T11$_3$ (1 mg/kg, i.v.) together with IL2/anti-T3 activated human PBL's ($1x10^7$ cells/d, i.v. x 3) was evaluated in the i.v. Namalwa model of SCID mice under different treatment protocols. Mice were injected i.v. with Namalwa cells ($4x10^5$) and treated either 1 h or 24 h later with the heterodimeric conjugate. Beginning 24 h after conjugate administration, both sets of animals were given 3 daily injections of PBL's. N901-anti-T11$_3$ which does not bind to the tumor cells served as a control. All three antibody conjugates tested showed efficacy by significantly ($p < 0.05$) prolonging the life of animals, while no such effects were observed in the control groups. Calculations from cell titration curves indicated that up to 5.8 logs of tumor cells could be eliminated *in vivo*. These studies indicate that Anti-B4-bR, 5E9-Maytansinoid and Anti-B4-anti-T11$_3$ heterodimer plus human PBL's have the potential to increase survival times and to effect complete cures in 25% of mice with malignant disease.

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TARGETING THERAPY WITH ADRIAMYCIN-MONOCLONAL ANTIBODY (HAb18) CONJUGATE IN NUDE MICE WITH HUMAN HEPATOCELLULAR CARCINOMA XENOGRAFTS

Sui Yanfang, He Zhilong, Liu Yanfang, Chen Zhinan
Department of Pathology, Fourth Military Medical University, Xi'an 710032 P.R. CHINA

Adriamycin (ADM) was linked covalently to the murine monoclonal antibody (McAb) HAb18 against hepatocellular carcinoma via a dextran (DEX) T-40 bridge. The molar ratio of HAb18: DEX: ADM was 1:2.4:56 in the conjugate. It was confirmed by immunocytochemical staining and ELISA that the antigen binding capacity of HAb18 in the conjugate was well preserved. In vitro study indicated that the conjugate cytotoxicity to tumor target cell lines was selective. The radio-immunoimaging and distribution of the conjugate labelled with ^{125}I in the nude mice bearing human hepatocellular carcinoma showed that ^{125}I-HAb18-DEX-ADM conjugate was localized in the tumor site. The HAb18-DEX-ADM targeting therapy in nude mice bearing human hepatocellular carcinoma showed the following results: tumor decreased in size with partial necrosis, in contrast to the rapidly growing tumor in the control group ($P<0.05$). Our study suggested that targeting therapy with HAb18-DEX-ADM conjugate may be useful in the treatment of patients with hepatocellular carcinoma.

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L2           147 S L1(S)(ANTIBOD? OR IMMUNOGLOBULIN# OR MAB OR AB OR IMMUNO? OR
L3            47 S L2 AND PY<2000
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L24            7 S L23 AND AD<19991001
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L26            3 S L25 AND AD<19991001
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L28            5 S L17(S)TAMOXIFEN
L29            0 S L28 AND AD<19991001

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L43           24 S L42 AND PY<2001
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L58         1135 S L57(5A)(COMBINATION OR COMBINED)
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     FILE 'MEDLINE, BIOSIS, SCISEARCH, CANCERLIT, LIFESCI, BIOTECHDS, CAPLUS'
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L62          172 S ANTI(W)L60
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L69           22 S L68 AND PY<2000
L70           13 DUP REM L69 (9 DUPLICATES REMOVED)
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L10 ANSWER 37 OF 37 MEDLINE on STN
ACCESSION NUMBER: 94235907 MEDLINE
DOCUMENT NUMBER: 94235907 PubMed ID: 7910054
TITLE: Taxol (**paclitaxel**): a novel anti-**microtubule** agent with remarkable anti-neoplastic activity.
AUTHOR: Foa R; Norton L; Seidman A D
CORPORATE SOURCE: Dipartimento di Scienze Biomediche e Oncologia Umana, Sezione Clinica, Turin, Italy.
SOURCE: INTERNATIONAL JOURNAL OF CLINICAL AND LABORATORY RESEARCH, **(1994)** 24 (1) 6-14. Ref: 62
Journal code: 9206491. ISSN: 0940-5437.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940621
Last Updated on STN: 19960129
Entered Medline: 19940616

AB Taxol (**paclitaxel**), an anti-**microtubule** agent extracted from the needles and bark of the Pacific yew tree Taxus brevifolia, has shown a remarkable anti-neoplastic effect in human cancer in phase I studies and early phase II and III trials thus far conducted. This has been reported primarily in advanced ovarian and breast cancer, although significant activity has also been documented in small-cell and non-small-cell lung cancer, head and neck cancers, and with lower activity in metastatic melanoma. The clinical utilization of Taxol had been previously somewhat restricted by its limited availability, a limitation that has recently been overcome by combined efforts of pharmaceutical, agricultural, and governmental agencies. In this review we shall address the pre-clinical data which have led to the use of Taxol in man, the main clinical results thus far obtained, the toxicities associated with its use, current ongoing trials and future clinical directions of this promising agent.

L22 ANSWER 1 OF 5 CANCERLIT on STN
ACCESSION NUMBER: 1999701330 CANCERLIT
DOCUMENT NUMBER: 99701330
TITLE: Combined and Sequential Paclitaxel-Based Chemosensitivity in Bladder Cancer Cell Lines. (Meeting abstract).
AUTHOR: McClellan William; DeHaven J I; Riggs D R; Hogan T F; Lamm D L
CORPORATE SOURCE: Department of Medicine, West Virginia University School of Medicine, Morgantown, WV.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1999)** 18 A1336.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616

AB Paclitaxel (P) is one of the most active investigational agents against advanced bladder carcinoma. We hypothesized that better responses and reduced toxicity might be achieved by combining **Paclitaxel**, an anti-**microtubule** agent with other chemotherapeutic agents (simultaneously or sequentially) that affected DNA replication (Carboplatin, CP) or microtubule function (Mitomycin C, MMC; Navelbine, N). Drug combinations have the potential advantage of additive or **synergistic** efficacy. Human bladder cancer cell lines (HTB9, **p53**+; T24, **p53**-), were plated in 96-well formats, 6 replicate wells/datapoint. Combinations included IC30-50 concentrations of secondary drugs (CP, MMC, N) added simultaneously with, 1 hour pre-, or 1 hour post-Paclitaxel administration. The MTT assay was used to evaluate cytotoxicity. [EMBEDDED TABLE] were **p<0.001, ***p<0.004, ****p<0.04. All drug combinations were significantly more cytotoxic than single agents, regardless of cell line **p53** status. Relative time of drug addition to **combination** treatments did not affect outcome. **Combination** treatments with P/CP, P/MMC, and P/N should be evaluated for efficacy and toxicity in vivo.

L70 ANSWER 8 OF 13 CANCERLIT on STN
ACCESSION NUMBER: 97618986 CANCERLIT
DOCUMENT NUMBER: 97618986
TITLE: Maximizing the therapeutic window of the anticarcinoma single-chain immunotoxin BR96 sFv-PE40 (Meeting abstract).
AUTHOR: Siegall C B; Chace D; Mixan B; Sugai J; Linsley P S; Haggerty H; Warner G; Davidson T
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute Seattle,WA 98121 USA Bristol-Myers Squibb Pharmaceutical Research Institute,Syracuse NY 13026 USA.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)** 38 A185.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB The single-chain **immunotoxin** BR96 sFv-PE40 which binds to the Le(y) antigen is a potent antitumor agent that has been shown to cure established human carcinoma xenografts implanted in mice and rats. BR96 sFv-PE40 is presently being evaluated in a Phase I clinical trial. Therapeutic efficacy of **immunotoxins** is a function of their antitumor efficacy versus their dose-limiting toxicities. We have examined the two most limiting toxicities of BR96 sFv-PE40, immunogenicity and vascular leak syndrome. BR96 sFv-PE40 is immunogenic in mice, rats and dogs by approx 10 days post administration. The concomitant administration of BR96 sFv-PE40 and the immunosuppressive agents deoxyspergualin, dexamethasone or CTLA4-lg have resulted in the reduction of anti-**immunotoxin** antibodies which can induce rapid clearance of the **immunotoxin** and potential kidney toxicities. Vascular-leak syndrome (VLS) has limited many **immunotoxin** clinical trials specifically through the formation of pulmonary edema. Using rats in which high dose BR96 sFv-PE40 induces VLS and pulmonary edema, prophylactic administration of anti-inflammatory agents including NSAIDs, dexamethasone and PLA2 inhibitors was found to inhibit VLS. Finally combination therapy of BR96 sFv-PE40 and the chemotherapeutic agent **paclitaxel** were found to induce greater antitumor affects in rodents carrying large tumor burdens than either agent alone and without increasing overall toxicity. In summary these studies can be used as guides in the attempt to maximize the therapeutic window of BR96 sFv-PE40 and other **immunotoxins**.

L9 ANSWER 3 OF 7 CANCERLIT on STN
ACCESSION NUMBER: 96650039 CANCERLIT
DOCUMENT NUMBER: 96650039
TITLE: Cure of large human colon cancer xenografts by a C242-Maytansinoid conjugate (Meeting abstract).
AUTHOR: Liu C; Widdison W; Chari R; Bourret L; Kedersha N; Ariniello P; Lambert J M; Blattler W A
CORPORATE SOURCE: ImmunoGen, Inc., Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1996)** 37 A3183.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB **Maytansinoids** are anticancer drugs that are 100- to 1000-fold more cytotoxic in vitro than anticancer drugs currently in clinical use. The **immunoconjugate**, C242-May, was prepared by **conjugating** approximately four **maytansinoid** drugs to the monoclonal **antibody** C242 which binds a mucin-type glycoprotein antigen expressed strongly on 60-70% of human colorectal cancers. C242-May was evaluated for antitumor activity and specificity in vitro and in vivo against the human colon carcinoma cell lines, COLO 205 (homogeneous antigen expression), LoVo and HT-29 (heterogeneous antigen expression). The **immunoconjugate** showed high antigen-specific cytotoxicity for the cultured tumor cells (IC50 = 5 to 50 pM). In vivo, iv administration of **conjugated maytansinoid** at a dose of 300 ug/kg/d x 5 induced complete regressions of established LoVo and HT-29 xenografts and cured large COLO 205 xenograft (300-500 mm3) growing subcutaneously in SCID mice. Comparison of the therapeutic results with 5-fluorouracil suggest that the therapeutic efficacy of C242-May **immunoconjugates** is superior to that of standard **chemotherapy** for treatment of colorectal cancer and is very promising for clinical evaluation.

L9 ANSWER 2 OF 7 CANCERLIT on STN
ACCESSION NUMBER: 97618990 CANCERLIT
DOCUMENT NUMBER: 97618990
TITLE: Cure of human small cell lung cancer xenografts in SCID mice by a hN901-maytansinoid immunoconjugate (Meeting abstract).
AUTHOR: Liu C; Bourret L A; Derr S M; Widdison W C; Lambert J M; Blattler W A; Chari R V
CORPORATE SOURCE: lmmunoGen Inc, Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)** 38 A190.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Changing the in vivo distribution of cytotoxic agents through **conjugating** to tumor-associated monoclonal **antibodies** may allow the introduction of novel more potent agents for the treatment of cancer which hold the promise of increased anticancer efficacy.The **maytansinoid** drug DM1 is in vitro a more potent cytotoxic agent by 100- to 1000-fold than anticancer drugs currently in clinical use. We have previously shown that **conjugation** of DM1 to monoclonal **antibodies** renders it a highly efficacious agent against cancers of breast and colon. Here we demonstrate its effectiveness on small cell lung cancers (SCLC) when **conjugated** to hN901 a humanized monoclonal **antibody** that targets CD56 which is expressed on all SCLC. The **immunoconjugate** hN901-DM1 was evaluated for antitumor activity and specificity in vitro and in vivo against the human SCLC cell lines SW2 and N417. hN901-DM1 showed high antigen-specific cytotoxicity for the cultured SCLC cells(IC50 = 6 x 10(-11) M). In vivo iv administration of hN901-DM1 at a **conjugated** DM1 dose of 300 ug/kg/d x 5 cured all mice bearing subcutaneous SCLC xenografts while the currently used drugs for SCLC **cisplatin** and etoposide either used as single agents or in combination at their maximum tolerated doses only moderately delayed the tumor growth. The preclinical results indicate that hN901-DM1 is a promising agent that may be worthy of clinical evaluation.

L45 ANSWER 5 OF 11 CANCERLIT on STN
ACCESSION NUMBER: 95610202 CANCERLIT
DOCUMENT NUMBER: 95610202
TITLE: Cure of human colon cancer xenografts by a C242-Maytansinoid conjugate (Meeting abstract).
AUTHOR: Liu C; Tadayoni M; Chari R; Grismore D; Bourret L; Goldmacher V; Ariniello P; Lambert J M; Blattler W A
CORPORATE SOURCE: ImmunoGen, Inc., Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1995)** 36 A2428.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950809
Last Updated on STN: 19950809

AB **Maytansinoids** are **anticancer** drugs that have 100- to 1000-fold higher cytotoxic potency than **anticancer** drugs currently in clinical use. An **immunoconjugate** (C242-May) was prepared by **conjugating** a **maytansinoid** with the monoclonal **antibody** C242. The **antibody** binds a mucin-type glycoprotein antigen which is expressed on 60-70% of colorectal cancers. The C242-May was evaluated for **antitumor** activity and specificity in vitro and in vivo against the human colon carcinoma cell lines, COLO 205 (homogeneous antigen expression), LoVo and HT-29 (heterogeneous antigen expression). The **immunoconjugate** showed high antigen-specific cytotoxicity for the cultured tumor cells (IC50, 5 pM to 50 pM). In vivo, iv administration of **conjugated maytansinoid** at a dose of 300 ug/kg/d x 5 induced complete regressions of established LoVo and HT-29 xenografts and cured COLO 205 xenograft growing subcutaneously in SCID mice. Mixtures consisting of an equivalent dose of C242 **antibody** and the free **maytansinoid,** or a nonbinding control **immunoconjugate,** had only very limited or no effect on the growth of the tumor xenografts. These results indicate that C242-May **immunoconjugates** may be worthy of clinical evaluation.

L45 ANSWER 1 OF 11 CANCERLIT on STN
ACCESSION NUMBER: 97618990 CANCERLIT
DOCUMENT NUMBER: 97618990
TITLE: Cure of human small cell lung cancer xenografts in SCID mice by a hN901-maytansinoid immunoconjugate (Meeting abstract).
AUTHOR: Liu C; Bourret L A; Derr S M; Widdison W C; Lambert J M; Blattler W A; Chari R V
CORPORATE SOURCE: lmmunoGen Inc, Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)** 38 A190.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Changing the in vivo distribution of cytotoxic agents through **conjugating** to tumor-associated monoclonal **antibodies** may allow the introduction of novel more potent agents for the treatment of cancer which hold the promise of increased **anticancer** efficacy.The **maytansinoid** drug DM1 is in vitro a more potent cytotoxic agent by 100- to 1000-fold than **anticancer** drugs currently in clinical use. We have previously shown that **conjugation** of DM1 to monoclonal **antibodies** renders it a highly efficacious agent against cancers of breast and colon. Here we demonstrate its effectiveness on small cell lung cancers (SCLC) when **conjugated** to hN901 a humanized monoclonal **antibody** that targets CD56 which is expressed on all SCLC. The **immunoconjugate** hN901-DM1 was evaluated for **antitumor** activity and specificity in vitro and in vivo against the human SCLC cell lines SW2 and N417. hN901-DM1 showed high antigen-specific cytotoxicity for the cultured SCLC cells(IC50 = 6 x 10(-11) M). In vivo iv administration of hN901-DM1 at a **conjugated** DM1 dose of 300 ug/kg/d x 5 cured all mice bearing subcutaneous SCLC xenografts while the currently used drugs for SCLC cisplatin and etoposide either used as single agents or in combination at their maximum tolerated doses only moderately delayed the tumor growth. The preclinical results indicate that hN901-DM1 is a promising agent that may be worthy of clinical evaluation.

L76 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:634868 CAPLUS
TITLE: Development of taxoids for use as **immunoconjugates**
AUTHOR(S): Miller, Michael L.; Roller, Elizabeth E.; Baloglu, Erkan; Leece, Barbara A.; Goldmacher, Victor S.; **Chari, Ravi V. J.**
CORPORATE SOURCE: Department of Chemistry, ImmunoGen, Inc, Cambridge, MA, 02139, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-260. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB **Taxol**- and Taxotere- are considered to be two of the most important drugs in modern cancer chemotherapy, being one of the std. treatments for breast cancer, non-small cell lung cancer, and ovarian cancer. Despite their widespread use in the treatment of these cancers, the therapeutic efficiency of these drugs is limited due to their non-specific toxicity to healthy tissues. One method to potentially overcome this lack of specificity is with the use of monoclonal antibodies directed against specific tumor-assocd. antigens. In our studies, we have focused on the development of novel taxoids that possess high potency, aq. soly., and a handle allowing them to be linked to antibodies useful in targeted delilvery. The synthesis, biol. applications, and development of a lead taxoid will be reviewed.

L81 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:230393 BIOSIS
DOCUMENT NUMBER: PREV199799529596
TITLE: Cure of human small cell lung cancer xenografts in SCID mice by a hN901-maytansinoid **immunoconjugate**.
AUTHOR(S): Liu, C.; Bourret, L. A.; Derr, S. M.; Widdison, W. C.; Lambert, J. M.; Blattler, W. A.; **Chari, R. V. J.**
CORPORATE SOURCE: ImmunoGen Inc., Cambridge, MA 02139, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 29.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research. San Diego, California, USA. April 12-16, 1997.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jun 1997
Last Updated on STN: 2 Jun 1997

L81 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:257283 BIOSIS
DOCUMENT NUMBER: PREV199698813412
TITLE: Cure of large human colon cancer xenografts by a C242-Maytansinoid conjugate.
AUTHOR(S): Liu, C.; Widdison, W.; **Chari, R.**; Bourret, L.; Kedersha, N.; Ariniello, P.; Lambert, J. M.; Blattler, W. A.
CORPORATE SOURCE: ImmunoGen Inc., Cambridge, MA 02139, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 466-467.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research. Washington, D.C., USA. April 20-24, 1996.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 1996
Last Updated on STN: 31 May 1996

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L45 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:123468 CAPLUS
DOCUMENT NUMBER: 126:216487
TITLE: The development of antibody delivery systems to target cancer with highly potent maytansinoids
AUTHOR(S): Liu, Changnian; Chari, Ravi V. J.
CORPORATE SOURCE: ImmunoGen, Inc., Cambridge, MA, 02139-4239, USA
SOURCE: Expert Opinion on Investigational Drugs (**1997**), 6(2), 169-172
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 18 refs. Improving the tumor selectivity of cytotoxic drugs through conjugation to tumor-reactive monoclonal antibodies may lead to novel, more potent agents for cancer therapy. The maytansinoid drugs are 100- to 1000-fold more cytotoxic in vitro than current clin. anticancer drugs. The authors recently demonstrated that conjugation of maytansinoid drugs to monoclonal antibodies renders them highly efficacious against cancers of breast and colon in both in vitro and in in vivo tumor models. Antibody-maytansinoids represent a new generation of immunoconjugates that may yet fulfil the promise of effective cancer therapy through antibody targeting of cytotoxic agents.

L45 ANSWER 3 OF 11 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 1
ACCESSION NUMBER: 96:588619 SCISEARCH
THE GENUINE ARTICLE: VB325
TITLE: ERADICATION OF LARGE COLON-TUMOR XENOGRAFTS BY TARGETED DELIVERY OF MAYTANSINOIDS
AUTHOR: LIU C N (Reprint); TADAYONI B M; BOURRET L A; MATTOCKS K M; DERR S M; WIDDISON W C; KEDERSHA N L; ARINIELLO P D; GOLDMACHER V S; LAMBERT J M; BLATTLER W A; CHARI R V J
CORPORATE SOURCE: IMMUNOGEN INC, 148 SIDNEY ST, CAMBRIDGE, MA, 02139 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (**06 AUG 1996**) Vol. 93, No. 16, pp. 8618-8623.
ISSN: 0027-8424.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **maytansinoid** drug DMI is 100- to 1000-fold more cytotoxic than **anticancer** drugs that are currently in clinical use. The **immunoconjugate** C242-DM1 was prepared by **conjugating** DMI to the monoclonal **antibody** C242, which recognizes a mucin-type glycoprotein expressed to various extents by human colorectal cancers, C242-DM1 was found to be highly cytotoxic toward cultured colon cancer cells in an antigen-specific manner and showed remarkable **antitumor** efficacy in vivo. C242-DM1 cured mice bearing subcutaneous COLO 205 human colon tumor xenografts (tumor size at time of treatment 65-130 mm(3)), at doses that shelved very little toxicity and were well below the maximum tolerated dose. C242-DM1 could even effect complete regressions or cures in animals with large (260- to 500-mm(3)) COLO 205 tumor xenografts. Further, C242-DM1 induced complete regressions of subcutaneous LoVo and HT-29 colon tumor xenografts that express the target antigen in a heterogeneous manner, C242-DM1 represents a new generation of **immunoconjugates** that may yet fulfill the promise of effective cancer therapy through **antibody** targeting of cytotoxic agents.

L45 ANSWER 7 OF 11 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 92083515 MEDLINE
DOCUMENT NUMBER: 92083515 PubMed ID: 1727373
TITLE: **Immunoconjugates** containing novel **maytansinoids**: promising **anticancer** drugs.
AUTHOR: Chari R V; Martell B A; Gross J L; Cook S B; Shah S A; Blattler W A; McKenzie S J; Goldmacher V S
CORPORATE SOURCE: ImmunoGen, Inc., Cambridge, Massachusetts 02139.
SOURCE: CANCER RESEARCH, **(1992 Jan 1)** 52 (1) 127-31.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199201
ENTRY DATE: Entered STN: 19920209
Last Updated on STN: 19970203
Entered Medline: 19920117

AB The potential of immunoconjugates of cytotoxic drugs for the treatment of cancer has not yet been realized owing to the difficulty of delivering therapeutic concentrations of these drugs to the target cells. In an effort to overcome this problem we have synthesized maytansinoids that have 100- to 1000-fold higher cytotoxic potency than clinically used anticancer drugs. These maytansinoids are linked to antibodies via disulfide bonds, which ensures the release of fully active drug inside the cells. The conjugates show high antigen-specific cytotoxicity for cultured human cancer cells (50% inhibiting concentration, 10 to 40 pM), low systemic toxicity in mice, and good pharmacokinetic behavior.

L70 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:262465 CAPLUS
DOCUMENT NUMBER: 126:325103
TITLE: Synergy of Taxol and radioimmunotherapy with yttrium-90-labeled chimeric L6 antibody: efficacy and toxicity in breast cancer xenografts
AUTHOR(S): De Nardo, Sally J.; Kukis, Daivd L.; Kroger, Linda A.; O'Donnell, Robert T.; Lamborn, Kathleen R.; Miers, Laird A.; De Nardo, Daivd G.; Meares, Claude F.; De Nardo, Gerald L.
CORPORATE SOURCE: Department Internal Medicine, University California Davis Medical Center, Sacramento, CA, 95816, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1997**), 94(8), 4000-4004
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Synergistic multimodality therapy is needed for breast cancer. Breast cancer frequently has p53 mutations that result in cells less likely to undergo apoptosis when exposed to DNA damaging therapies. Taxol (paclitaxel) is more effective in the presence of mutant p53. 90Y-labeled DOTA-peptide-ChL6 (90Y-ChL6, where ChL6 is chimeric L6 antibody and DOTA is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) is a novel radioimmunoconjugate for targeting radiation to cancer. It has a stable metal chelator and a peptide linker that can be catabolized by hepatic lysozymes. This study was designed to assess potential synergism between Taxol and 90Y-ChL6 in a highly anaplastic breast cancer model, HBT 3477. There was no tumor response in mice receiving ChL6 or Taxol alone. In mice receiving 90Y-ChL6 alone, 79% (15 of 19) of tumors responded although none were cured. If Taxol was administered 24-72 h before 90Y-ChL6, again, 79% (23 of 29) of tumors responded but 21% were cured. When Taxol was administered 6 or 24 h after 90Y-ChL6, 100% (46 of 46) of tumors responded and 48% were cured. Taxol given with 90Y-ChL6 did not substantially increase toxicity. Enhancement of the therapeutic effect when Taxol was added to 90Y-ChL6 therapy for HBT 3477 xenografts was striking. The synergistic therapeutic effect of Taxol with 90Y-ChL6 may relate to the p53 mutant status and BCL2 expression in HBT 3477 cells, observations that increase the likelihood that the results of this study are relevant to therapy for breast cancer in patients. In conclusion, Taxol seemed to be synergistic with 90Y-ChL6 in this human breast cancer model. Up to 50% of these anaplastic breast cancer xenografts were cured by combined modality therapy.

L70 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:222491 CAPLUS
DOCUMENT NUMBER: 124:250918
TITLE: Novel mutant BR96 monoclonal antibodies, their production using plasmids, and their application as immunoconjugates with cytotoxic agents in human carcinoma treatment
INVENTOR(S): Yelton, Dale; Glaser, Scott; Huse, William; Rosok, Mae Joanne
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: Eur. Pat. Appl., 91 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
EP 699756	A1	19960306	EP 1995-305444	19950803	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
US 5728821	A	19980317	US 1994-285936	19940804	<--
US 5792456	A	19980811	US 1995-487860	19950607	<--

PRIORITY APPLN. INFO.: US 1994-285936 A 19940804
US 1995-487860 A 19950607

AB The present invention provides mutant BR96 polypeptides (and cDNAs encoding them) having a variable region comprising an amino acid sequence substantially homologous to the variable region of monoclonal antibody BR96. Immunoconjugates, BR96 mutants conjugated with cytotoxic agents have applications in treatments of human carcinomas.

L45 ANSWER 6 OF 11 CANCERLIT on STN
ACCESSION NUMBER: 94697589 CANCERLIT
DOCUMENT NUMBER: 94697589
TITLE: An immunotoxin, an antibody-drug conjugate and a heterodimeric antibody conjugate show tumor-specific efficacy in animal survival models (Meeting abstract).
AUTHOR: Shah S A; Ferris C A; Derr S M; Bourret L A; Chari R V; Venkatesh Y P; Goldmacher V S; Lambert J M; Blattler W A
CORPORATE SOURCE: ImmunoGen Inc., 148 Sidney St., Cambridge, MA 02139.
SOURCE: Antibody Immunoconjugates Radiopharmaceuticals, **(1993)** 6 (1) 69.
ISSN: 0892-7049.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19970509

AB The therapeutic efficacies of an **immunotoxin**, an **antibody**-drug **conjugate** and a heterodimeric **antibody conjugate** (with activated human PBLs) were assessed in xenograft mouse tumor models. Anti-CD19 monoclonal **antibody**, anti-B4, **conjugated** to blocked ricin (anti-B4-bR, 50 or 75 ug/kg/d iv x 5) was evaluated in SCID mice bearing 7 d established human B-cell lymphoma (4 x 10(6) Namalwa cells, iv). Controls included treatment with unconjugated anti-B4 **antibody** (2 mg/kg/d iv x 5) or a nonspecific **antibody**-blocked ricin **conjugate** (N901-bR, 100 ug/kg/d iv x 5). Anti-transferrin receptor **antibody**, 5E9, **conjugated** to a **maytansinoid** (5E9-**Maytansinoid**, 7 mg/kg/d, on days 1, 3, 5) was injected iv in SCID mice one hour after ip injection of A375 human melanoma cells (3.5 x 10(7)). Three iv injections of a mixture of unconjugated 5E9 **antibody** (15 mg/kg/d x 3) plus free **maytansinoid** drug (0.11 mg/kg/d x 3) served as a control. The **antitumor** efficacy of a heterodimeric **conjugate**, anti-B4-anti-T11(3) (1 mg/kg iv) together with IL2/anti-T3 activated human PBLs (1 x 10(7) cells/d iv x 3) was evaluated in the iv Namalwa model of SCID mice under different treatment protocols. Mice were injected iv with Namalwa cells (4 x 10(5)) and treated either 1 hr or 24 hr later with the heterodimeric **conjugate**. Beginning 24 hr after **conjugate** administration, both sets of animals were given 3 daily injections of PBLs. N901-anti-T11(3), which does not bind to the tumor cells, served as a control. All three **antibody conjugates** tested showed efficacy by significantly (p less than 0.05) prolonging the life of animals, while no such effects were observed in the control groups. Calculations from cell titration curves indicated that up to 5.8 logs of tumor cells could be eliminated in vivo. These studies indicate that anti-B4-bR, 5E9-**maytansinoid** and anti-B4-anti-T11(3) heterodimer plus human PBLs have the potential to increase survival times and to effect complete cures in 25% of mice with malignant disease.

L13 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 92314067 MEDLINE
DOCUMENT NUMBER: 92314067 PubMed ID: 1616951
TITLE: Properties of chimeric toxins with two recognition domains: interleukin 6 and transforming growth factor alpha at different locations in Pseudomonas exotoxin.
AUTHOR: Kreitman R J; Siegall C B; Chaudhary V K; FitzGerald D J; Pastan I
CORPORATE SOURCE: Laboratory of Molecular Biology, DCBDC, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.
SOURCE: BIOCONJUGATE CHEMISTRY, (1992 Jan-Feb) 3 (1) 63-8. Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920815
Last Updated on STN: 20000303
Entered Medline: 19920805

AB Pseudomonas exotoxin (PE) is a potent cytotoxic agent that is composed of 613 amino acids arranged into three major domains. We have previously identified two positions where ligands can successfully be placed in PE to direct it to cells with specific surface receptors. One site is at the amino terminus and the other is close to but not at the C-terminus. To examine the possibility of constructing oncotoxins with two different recognition elements that will bind to two different receptors, we have placed cDNAs encoding either transforming growth factor alpha (TGF alpha) or interleukin 6 (IL6) at the 5' end of a PE gene and also inserted a cDNA encoding TGF alpha near the 3' end of the PE gene. The plasmids encoding these chimeric toxins were expressed in Escherichia coli and the chimeric proteins purified to near homogeneity. In all the new toxins, the TGF alpha near the C-terminus was inserted after amino acid 607 of PE and followed by amino acids 604-613 so that the correct PE C-terminus (REDLK) was preserved. For each chimera, the toxin portion was either PE4E, in which the cell binding domain (domain Ia) is mutated, **PE40**, in which domain Ia is **deleted**, or PE38, in which domain Ia and part of domain Ib are deleted. These derivatives of PE do not bind to the PE receptor and allow 607, 355, or 339 amino acids, respectively, between the two ligands.(ABSTRACT TRUNCATED AT 250 WORDS)

L5 ANSWER 73 OF 87 MEDLINE on STN DUPLICATE 30
ACCESSION NUMBER: 96362743 MEDLINE
DOCUMENT NUMBER: 96362743 PubMed ID: 8729950
TITLE: Phase II trial of taxol in patients with adenocarcinoma of the upper gastrointestinal tract (UGIT). The Eastern Cooperative Oncology group (ECOG) results.
AUTHOR: Einzig A I; Lipsitz S; Wiernik P H; Benson A B 3rd
CORPORATE SOURCE: Department of Medicine, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
SOURCE: INVESTIGATIONAL NEW DRUGS, **(1995)** 13 (3) 223-7.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 19961106
Entered Medline: 19961021

AB Taxol was administered as a 24-hour continuous infusion at 250 mg/m2 in this Phase II trial in patients with adenocarcinomas of the upper gastrointestinal tract (UGIT). Twenty-five patients were entered between July 1991 and June 1992, twenty-three were eligible and were evaluated for toxicity and twenty-two were assessable for response. There was one partial response (4.5%) in a patient with liver metastases, with a duration of 6 months. Toxicity was primarily neutropenia. **Taxol** as a **single agent** appears to have little activity in adenocarcinoma of the UGIT.

L12 ANSWER 8 OF 55 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 4
ACCESSION NUMBER: 1998:275650 BIOSIS
DOCUMENT NUMBER: PREV199800275650
TITLE: Natural organic compounds that affect to microtubule functions.
AUTHOR(S): Iwasaki, Shigeo [Reprint author]
CORPORATE SOURCE: Kitasato Inst., 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
SOURCE: Yakugaku Zasshi, (April, 1998) Vol. 118, No. 4, pp. 111-126. print.
CODEN: YKKZAJ. ISSN: 0031-6903.
DOCUMENT TYPE: Article
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 24 Jun 1998
Last Updated on STN: 13 Aug 1998

AB Microtubules (MT), composed of a protein tubulin (TN) alpha,beta-heterodimer with concomitant other proteins, microtubule associated proteins (MAPs and tau), are known to be the main component of spindles in a mitotic apparatus of eucaryotic cells, and are also involved in many other basic and essential cell functions. There are a number of natural and synthetic compounds that interfere with MT function to cause the mitotic arrest of eucaryotic cells. Such antimitotic agents show a broad biological activity, and can be used for medicinal and agrochemical purposes. On the other hand, they are also important as the biochemical tools for understanding the dynamics of MT network. Most of such antimitotic agents, with a few exceptions, bind to beta-TN. Among them, colchicine (CLC), vinblastine (VLB) and **taxol** have been of major importance in biochemical studies of MT and in studies of their intracellular functions. The former two both inhibit MT assembly but their binding sites on 8-TN are different; CLC-site and VLB-site, and many MT inhibitors bind to either sites. **Taxol** bind to TN at a site other than CLC-site and VLB-site, and promote MT assembly. We have worked on a variety of antimitotic agents that bind to CLC, VLB or **taxol** -site, in discoveries, structures, biological actions and/or interactions with TN. In this paper, I summarized the results of our studies on VLB-site ligands; (1) rhizoxin (RZX), isolated as a phytotoxin produced by a plant pathogenic fungus, and its related compounds, (2) derivatives of ansamitocin P-3 (ASMP3) (**maytansinoid**: MAY), isolated as a cytotoxic metabolite of an Actinomycete, (3) phomopsin A (PMSA), isolated as a mycotoxin produced by a plant parasitic fungus, (4) dolastatin 10 (DLS10), isolated as a cytotoxic metabolite of a see animal, (5) ustiloxins (USL) A-F, isolated as a mycotoxin produced by a plant pathogenic fungus, (6) arenastatin A (ARSA), isolated as a cytotoxic metabolite of a sponge, and its synthetic analogs. From our studies on interactions of these VLB-site ligands with TN, we showed that the presence of a distinct RZX/MAY-binding site which only partially overlap with VLB-site, and that PMSA, DLS10, USLs and ARSA bind to the RZX/MAY site. RZX, ASMP3 and ARSA inhibit the growth of a variety of fungi, including Aspergillus nidulans. In order to obtain information as to the drug-TN interaction at the RZX/MAY site, RZX-resistant 8-TN gene mutants were isolated from RZX-sensitive wild-type A. nidulans. In all the beta-TN gene mutants, single amino acid (100th) alteration, asparagine-to-isoleucine, was observed. Sequence displacement experiments confirmed that this alteration conferred resistance to RZX and ASMP3, and also to ARSA. This resistance mechanism was further verified with yeasts Schizosaccharomyces pombe and Saccharomyces cerevisiae. All the natural ligands mentioned above show potent cytotoxicity against human and murine tumor cells, but VLB, PMSA, DLS10 and USLA are inactive to both RZX-sensitive and -resistant fungal strains.

L2 ANSWER 10 OF 10 CANCERLIT on STN
ACCESSION NUMBER: 97618986 CANCERLIT
DOCUMENT NUMBER: 97618986
TITLE: Maximizing the therapeutic window of the anticarcinoma single-chain immunotoxin BR96 sFv-PE40 (Meeting abstract).
AUTHOR: **Siegall C B**; Chace D; Mixan B; Sugai J; Linsley P S; Haggerty H; Warner G; Davidson T
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute Seattle,WA 98121 USA Bristol-Myers Squibb Pharmaceutical Research Institute,Syracuse NY 13026 USA.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)** **38** A185.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB The single-chain immunotoxin BR96 sFv-PE40 which binds to the Le(y) antigen is a potent antitumor agent that has been shown to cure established human carcinoma xenografts implanted in mice and rats. BR96 sFv-PE40 is presently being evaluated in a Phase I clinical trial. Therapeutic efficacy of immunotoxins is a function of their antitumor efficacy versus their dose-limiting toxicities. We have examined the two most limiting toxicities of BR96 sFv-PE40, immunogenicity and vascular leak syndrome. BR96 sFv-PE40 is immunogenic in mice, rats and dogs by approx 10 days post administration. The concomitant administration of BR96 sFv-PE40 and the immunosuppressive agents deoxyspergualin, dexamethasone or CTLA4-lg have resulted in the reduction of anti-immunotoxin antibodies which can induce rapid clearance of the immunotoxin and potential kidney toxicities. Vascular-leak syndrome (VLS) has limited many immunotoxin clinical trials specifically through the formation of pulmonary edema. Using rats in which high dose BR96 sFv-PE40 induces VLS and pulmonary edema, prophylactic administration of anti-inflammatory agents including NSAIDs, dexamethasone and PLA2 inhibitors was found to inhibit VLS. Finally combination therapy of BR96 sFv-PE40 and the chemotherapeutic agent paclitaxel were found to induce greater antitumor affects in rodents carrying large tumor burdens than either agent alone and without increasing overall toxicity. In summary these studies can be used as guides in the attempt to maximize the therapeutic window of BR96 sFv-PE40 and other immunotoxins.

L33 ANSWER 60 OF 62 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 94226963 MEDLINE
DOCUMENT NUMBER: 94226963 PubMed ID: 7909688
TITLE: **Clinical**, toxicological and pharmaceutical aspects of the antineoplastic drug **taxol**: a review.
AUTHOR: Guchelaar H J; ten Napel C H; de Vries E G; Mulder N H
CORPORATE SOURCE: Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede, The Netherlands.
SOURCE: CLINICAL ONCOLOGY (ROYAL COLLEGE OF RADIOLOGISTS), **(1994)** 6 (1) 40-8. Ref: 81
Journal code: 9002902. ISSN: 0936-6555.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940620
Last Updated on STN: 19950206
Entered Medline: 19940609

AB **Taxol**, a diterpene alkaloid isolated from the bark of Taxus brevifolia, has a unique mechanism of action. The drug promotes the formation of microtubule polymers in a cell, by reversibly and specifically binding the beta-subunit of tubulin. **Taxol** is administered intravenously by a 3-24-hour infusion at 3-week intervals. Myelosuppression, especially neutropenia, appears to be the dose limiting toxicity in solid tumours at 200-250 mg/m2. Furthermore, side effects such as sensory neurotoxicity (with typical numbness, tingling and painful paraesthesiae in the extremities), diarrhoea and alopecia appear frequently. Mucositis appears to be the non-haematological dose limiting side effect at 390 mg/m2 that has been determined in patients with leukaemia. Hypersensitivity reactions, which have been fatal in individual cases, might be schedule dependent. Furthermore, antiallergic prophylaxis must be given, although this precaution might not be considered to be fully protective. Phase I studies performed with combinations of **taxol** and cisplatin, doxorubicin or cyclophosphamide have indicated the feasibility of these regimens and show promise for future investigations. Addition of granulocyte-colony stimulating factor (G-CSF), aimed at modulating myelosuppressive toxicity, showed in Phase I studies that the **taxol** dose could be increased to 250 mg/m2, with peripheral neuropathy as the dose limiting toxicity. In Phase II studies, **taxol** has been shown to be effective, including producing complete tumour remission, in advanced drug refractory ovarian carcinoma (19%-36% response rate), previously treated patients with metastatic breast carcinoma (27%-62% response rate), advanced non-small lung cancer (21%-24% response rate), advanced **small cell lung cancer** (37% response rate) and advanced head and neck cancer (34% response rate).(ABSTRACT TRUNCATED AT 250 WORDS)

L14 ANSWER 1 OF 1 CANCERLIT on STN
ACCESSION NUMBER: 97610268 CANCERLIT
DOCUMENT NUMBER: 97610268
TITLE: Importance of microtubule stabilization in taxane induced cytotoxicity, apoptosis and growth factor gene induction in a human ovarian cancer cell line (Meeting abstract).
AUTHOR: Watson J M; Kingston D G; Chordia M D; Fulghum R A; Haskill J S
CORPORATE SOURCE: UNC Lineberger Comprehensive Cancer Center, Univ. of North Carolina, Chapel Hill, NC 27599-0212.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1996) 37 A2997. ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Taxol is a unique chemotherapeutic agent that promotes the stabilization of microtubules, arresting cells in G2/M and often inducing apoptosis in cancer cells in vitro. To identify a relationship between tubulin stabilization and other biological activities, we compared cytotoxicity, apoptosis and cytokine gene induction among 12 structurally related Taxol analogs using a human ovarian cancer cell line, OVCA 420. The results show that the analogs could be divided into 3 major groups: group 1, does not stabilize microtubules and was incapable of inducing gene induction or **cytotoxicity**; group 2, which includes **Taxol** and taxotere, **stabilized microtubules** and demonstrated moderate levels of gene induction and cytotoxicity involving apoptosis; group 3 compounds failed to stabilize tubulin but demonstrated high levels of gene induction and cytotoxicity. Surprisingly, the mechanism of cytotoxicity induced by group 3 analogs does not appear to involve apoptosis. We conclude that only apoptosis is dependent upon microtubule stabilization in taxane induced cytotoxicity. Additionally, while a correlative relationship exists between induced cytokine expression and cytotoxicity, the lack of apoptosis by group 3 but not group 2 analogs suggests multiple separate pathways of Taxol and/or taxane induced cytotoxicity.

L5 ANSWER 1 OF 26 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 97178765 MEDLINE
DOCUMENT NUMBER: 97178765 PubMed ID: 9053498
TITLE: Immunotoxin therapy of small-cell lung cancer: a phase I study of N901-blocked ricin.
AUTHOR: Lynch T J Jr; Lambert J M; Coral F; Shefner J; Wen P; Blattler W A; Collinson A R; Ariniello P D; Braman G; Cook S; Esseltine D; Elias A; Skarin A; Ritz J
CORPORATE SOURCE: Hematology-Oncology Unit, Massachusetts General Hospital, Boston 02114, USA.. Lynch.Thomas@mgh.harvard.edu
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, **(1997 Feb)** 15 (2) 723-34.
Journal code: 8309333. ISSN: 0732-183X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970310

AB PURPOSE: Immunotoxins could improve outcome in small-cell lung cancer (SCLC) by targeting tumor cells that are resistant to chemotherapy and radiation. N901 is a murine monoclonal antibody that binds to the CD56 (neural cell adhesion molecule [NCAM]) antigen found on cells of neuroendocrine origin, including SCLC. N901-bR is an immunoconjugate of **N901 antibody** with blocked ricin (bR) as the cytotoxic effector moiety. N901-bR has more than 700-fold greater selectivity in vitro for killing the CD56+ SCLC cell line SW-2 than for an antigen-negative lymphoma cell line. Preclinical studies suggested the potential for clinically significant cardiac and neurologic toxicity. We present a phase I study of N901-bR in relapsed SCLC. PATIENTS AND METHODS: Twenty-one patients (18 relapsed, three primary refractory) with SCLC were entered onto this study. Successive cohorts of at least three patients were treated at doses from 5 to 40 microg/kg/d for 7 days. The initial three cohorts received the first day's dose (one seventh of planned dose) as a bolus infusion before they began the continuous infusion on the second day to observe acute toxicity and determine bolus pharmacokinetics. Toxicity assessment included nerve-conduction studies (NCS) and radionuclide assessment of left ventricular ejection fraction (LVEF) before and after N901-bR administration to fully assess potential neurologic and cardiac toxicity. RESULTS: The dose-limiting toxicity (DLT) of N901-bR given by 7-day continuous infusion is capillary leak syndrome, which occurred in two of three patients at the dose of 40 microg/kg (lean body weight [LBW])/d. Detectable serum drug levels equivalent to effective in vitro drug levels were achieved at the 20-, 30-, and 40-microg/kg(LBW)/d dose levels. Specific binding of the immunotoxin to tumor cells in bone marrow, liver, and lung was observed. Cardiac function remained normal in 15 of 16 patients. No patient developed clinically significant neuropathy. However, a trend was noted for amplitude decline in serial NCS of both sensory and motor neurons. One patient with refractory SCLC achieved a partial response. CONCLUSION: N901-bR is an immunotoxin with potential clinical activity in SCLC. N901-bR is well tolerated when given by 7-day continuous infusion at the dose of 30 microg/kg(LBW)/d. Neurologic and cardiac toxicity were acceptable when given to patients with refractory SCLC. A second study to evaluate this agent after induction chemoradiotherapy in both limited- and extensive-stage disease was started following completion of this study.

L11 ANSWER 4 OF 6 CANCERLIT on STN
ACCESSION NUMBER: 97618990 CANCERLIT
DOCUMENT NUMBER: 97618990
TITLE: Cure of human small cell lung cancer xenografts in SCID mice by a **hN901-maytansinoid** immunoconjugate (Meeting abstract).
AUTHOR: Liu C; Bourret L A; Derr S M; Widdison W C; Lambert J M; Blattler W A; Chari R V
CORPORATE SOURCE: lmmunoGen Inc, Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A190.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Changing the in vivo distribution of cytotoxic agents through conjugating to tumor-associated monoclonal antibodies may allow the introduction of novel more potent agents for the treatment of cancer which hold the promise of increased anticancer efficacy.The **maytansinoid** drug DM1 is in vitro a more potent cytotoxic agent by 100- to 1000-fold than anticancer drugs currently in clinical use. We have previously shown that conjugation of DM1 to monoclonal antibodies renders it a highly efficacious agent against cancers of breast and colon. Here we demonstrate its effectiveness on small cell lung cancers (SCLC) when conjugated to **hN901** a humanized monoclonal antibody that targets CD56 which is expressed on all SCLC. The immunoconjugate **hN901**-DM1 was evaluated for antitumor activity and specificity in vitro and in vivo against the human SCLC cell lines SW2 and N417. **hN901**-DM1 showed high antigen-specific cytotoxicity for the cultured SCLC cells(IC50 = 6 x 10(-11) M). In vivo iv administration of **hN901**-DM1 at a conjugated DM1 dose of 300 ug/kg/d x 5 cured all mice bearing subcutaneous SCLC xenografts while the currently used drugs for SCLC cisplatin and etoposide either used as single agents or in combination at their maximum tolerated doses only moderately delayed the tumor growth. The preclinical results indicate that **hN901**-DM1 is a promising agent that may be worthy of clinical evaluation.

L4 ANSWER 6 OF 8 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:634208 SCISEARCH
THE GENUINE ARTICLE: 110NJ
TITLE: Tryprostatin A, a specific and novel inhibitor of microtubule assembly
AUTHOR: Usui T; Kondoh M; Cui C B; Mayumi T; Osada H (Reprint)
CORPORATE SOURCE: RIKEN, INST PHYS & CHEM RES, ANTIBIOT LAB, HIROSAWA 2-1, WAKO, SAITAMA 35101, JAPAN (Reprint); RIKEN, INST PHYS & CHEM RES, ANTIBIOT LAB, WAKO, SAITAMA 35101, JAPAN; OSAKA UNIV, FAC PHARMACEUT SCI, SUITA, OSAKA 565, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: BIOCHEMICAL JOURNAL, (1 AUG 1998) Vol. 333, Part 3, pp. 543-548.
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND.
ISSN: 0264-6021.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 44

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have investigated the cell cycle inhibition mechanism and primary target of tryprostatin A (TPS-A) purified from Aspergillus fumigatus. TPS-A inhibited cell cycle progression of asynchronously cultured 3Y1 cells in the M phase in a dose- and time-dependent manner. In contrast, TPS-B (the demethoxy analogue of TPS-A) showed cell-cycle non-specific inhibition on cell growth even though it inhibited cell growth at lower concentrations than TPS-A. TPS-A treatment induced the reversible disruption of the cytoplasmic microtubules of 3Y1 cells as observed by indirect immunofluorescence microscopy in the range of concentrations that specifically inhibited M-phase progression. TPS-A inhibited the assembly in vitro of microtubules purified from bovine brains (40 % inhibition at 250 mu M); however, there was little or no effect on the self-assembly of purified tubulin when polymerization was induced by glutamate even at 250 mu M TPS-A. TPS-A did not inhibit assembly promoted by taxol or by digestion of the C-terminal domain of tubulin. However, TPS-A blocked the tubulin assembly induced by inducers interacting with the C-terminal domain, microtubule-associated protein 2 (MAP2), tau and poly-(L-lysine). These results indicate that TPS-A is a novel inhibitor of MAP-dependent microtubule assembly and, through the disruption of the microtubule spindle, specifically inhibits cell cycle progression at the M phase.

than times observed for **vinblastine** or vinorelbine.
Sedimentation velocity experiments at low speeds and electron microscopy are consistent with the presence of a small amount of larger polymers (greater than or equal to 40S) in the vincristine samples, possibly involving alignment of spirals. Under our experimental conditions, these larger polymers appear to have a minimal effect on the estimated energetics of the vincristine-induced self-association of tubulin.

L28 ANSWER 38 OF 43 CANCERLIT on STN
ACCESSION NUMBER: 96625474 CANCERLIT
DOCUMENT NUMBER: 96625474
TITLE: The current status of taxol.
AUTHOR: Rowinsky E K; McGuire W P; Donehower R C
CORPORATE SOURCE: Division of Pharmacology and Experimental Therapeutics, Johns Hopkins Oncology Center, Baltimore, MD.
SOURCE: Prin Pract Gynecol Oncol Updates, **(1993)** 1 (1) 1-16.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB This overview covers the background and history of taxol (paclitaxel) and its isolation from the bark of the Pacific yew Taxus brevifolia. **Taxol** acts on cellular **microtubules**, which are involved in a wide range of functions including cell motility and maintenance of shape, intracellular transport, signal mediation, and mitosis. Taxol shifts the natural equilibrium of tubulin towards microtubule assembly, rather than dissolution as do the vinca alkaloids which associate primarily with tubulin dimers. Drug resistance in cell lines has been associated either with altered alpha- and beta-tubulin subunits that have impaired ability to polymerize, or with the mdr multidrug resistance phenotype involving amplification of the membrane p-glycoprotein drug-efflux pump, which is associated with cross-resistance to actinomycin D, colchicine, doxorubicin, and vinca alkaloids. Taxol was moderately active against L1210, P388, and P1534 leukemias, Walker 256 carcinosarcoma, sarcoma 180, Lewis lung carcinoma, and KB cells in culture, as well as a number of human xenografts. The preclinical toxicology is briefly reviewed. Fourteen Phase I single-agent trials are tabulated and summarized. The toxicities of taxol include: neutropenia, which is usually dose-limiting; hypersensitivity reactions such as dyspnea, bronchospasm, urticaria and rashes, seen in up to 84% of cases in some early trials (with premedication now around 3%), more frequent with 3-hr than 24-hr infusions, and associated with the Cremophor EL vehicle; mucositis; thrombocytopenia; myalgias; peripheral neuropathy; some cardiac rhythm disturbances, most commonly asymptomatic bradycardia, but also atrial arrhythmias, myocardial infarction, and ventricular tachyarrhythmias; nausea and vomiting; and diarrhea. In the blood, taxol is 95-98% protein-bound, with a steady-state volume of distribution of 55-59 L/m2, and beta-elimination half-life of 3.9-6.4 hours. Renal clearance accounts for only 1.4-6.6% of dose. Some 20% and 40% of the dose is cleared in the bile in rats and humans, respectively, and several hydroxylated metabolites are found. Five Phase II trials in advanced and refractory ovarian carcinoma are tabulated and described. Overall response rates of 20-50% were reported. In metastatic breast cancer, two trials produced overall responses of 56% and 62%. Other topics discussed include **combination** studies with cisplatin and G-CSF in breast and ovarian cancers, intraperitoneal **chemotherapy** of ovarian cancer, compassionate use in ovarian cancer patients, two trials in non-small-cell lung cancer (21 and 24% responses), initial study in head and neck cancer and other tumor types, and questions about drug supply and possible analogs. (113 References)

HE GENUINE ARTICLE: NB995
TITLE: CHARACTERIZATION OF A TAXOL-RESISTANT HUMAN SMALL-CELL LUNG-CANCER CELL-LINE

AUTHOR: OHTA S; NISHIO K; KUBOTA N; OHMORI T; FUNAYAMA Y; OHIRA T; NAKAJIMA H; ADACHI M; SAIJO N (Reprint)

CORPORATE SOURCE: NATL CANC CTR, RES INST, DIV PHARMACOL, TSUKIJI 5-1-1, CHUO KU, TOKYO 104, JAPAN (Reprint); NATL CANC CTR, RES INST, DIV PHARMACOL, TSUKIJI 5-1-1, CHUO KU, TOKYO 104, JAPAN; SHOWA UNIV, DEPT INTERNAL MED 1, SHINAGAWA KU, TOKYO 142, JAPAN

COUNTRY OF AUTHOR: JAPAN

SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (**MAR 1994**)
Vol. 85, No. 3, pp. 290-297.
ISSN: 0910-5050.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Taxol is a novel anticancer agent with activity against a broad range of tumors. It has a unique ability to stabilize polymerized tubulin into microtubule bundles within the cell. We have established a taxol-resistant human small-cell lung cancer cell line (H69/Txl) by exposing H69 cells to stepwise increases in taxol concentration. The resistance of H69/Txl cells to taxol was 4.7-fold that of the original H69 cells: the IC50 values for H69 and H69/Txl were 113.7 +/- 56.54 nM and 538.7 +/- 214.7 nM by the tetrazolium dye assay, respectively. Removal of the drug from the medium resulted in a 38% decrease in the growth rate of H69/Txl as compared with that in the presence of 30 nM taxol, suggesting that the growth of H69/Txl was partially dependent on taxol. H69/Txl showed higher sensitivity to vinca alkaloids such as vindesine, vincristine and **vinblastine** than the parental H69. There was no significant difference in intracellular [H-3]taxol content between H69 and H69/Txl cells. No MDR-1 mRNA was detected in H69/Txl by the reverse transcription polymerase chain reaction. There was no significant difference of total and polymerized tubulin content between H69 and H69/Txl cells. Altered mobility of one of the alpha-tubulin isoforms in H69/Txl was revealed by using isoelectric focusing and Western blotting with anti-alpha-tubulin antibody. In H69, two a-tubulin isoforms were observed, whereas three were evident in H69/Txl, two of them comigrating with the isoforms of H69 and the other being more acidic. We observed the **increased** acetylation of a-**tubulin** in H69/Txl cells as compared with that in H69 cells. The acetylation of alpha-tubulin may be responsible for the taxol resistance and/or taxol-dependent growth of H69/Txl.

L10 ANSWER 39 OF 43 CANCERLIT on STN
ACCESSION NUMBER: 95611692 CANCERLIT
DOCUMENT NUMBER: 95611692
TITLE: Regulation of chemoresistance by BCL-2 (Meeting abstract).
AUTHOR: Reed J C
CORPORATE SOURCE: La Jolla Cancer Research Foundation, La Jolla, CA 92037.
SOURCE: Ann Oncol, **(1994)** 5 (Suppl 5) A193.
ISSN: 0923-7534.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950906
Last Updated on STN: 19950906

AB The bcl-2 gene becomes activated by the t(14;18) chromosomal translocations that occur in the majority of non-Hodgkin's lymphomas, leading to overproduction of the 26-kD Bcl-2 protein. High levels of bcl-2 expression can also be found in the absence of detectable structural alterations in the bcl-2 gene in a wide variety of human cancers including breast, prostate, lung, **colorectal** and nasopharyngeal carcinomas, neuroblastomas, and some types of leukemia. To explore the molecular basis for the dysregulation of bcl-2 seen in many types of cancer, we investigated the regulatory elements within the bcl-2 gene using reporter gene assays. A p53-negative response element was discovered in the bcl-2 gene, suggesting that p53 loss may result in loss of repression of bcl-2 gene expression in cancer. Consistent with this hypothesis, expression of a temperature-sensitive version of p53 into a p53-deficient leukemia line resulted in down-regulation of bcl-2 mRNA and bcl-2 protein levels upon shift to the permissive temperature, followed by induction of apoptotic cell death. These findings link p53 and Bcl-2 in a pathway that regulates apoptosis. Previous studies showed that over-production of the Bcl-2 protein contributes to neoplastic cell expansion primarily by promoting cell survival through interference with programmed cell death (apoptosis). Because many chemotherapeutic drugs are capable of activating pathways leading to apoptotic cell death, we used gene transfer methods to achieve elevations in the levels of Bcl-2 protein in various neoplastic lymphoid cell lines as well as a human neuroblastoma line and then tested their relative resistance to killing by several drugs (both cell cycle-dependent and -independent) commonly used in the treatment of cancer, including: dexamethasone, methotrexate, Ara-C, VP16, cisplatin, vincristine, 4-HC, 2-CdA, Adriamycin, daunomycin and **Taxol**. Cells that had been stably infected with a recombinant bcl-2 retrovirus and that contained 5- to 20-fold elevated levels of Bcl-2 protein were strikingly more resistant to killing all drugs tested than cells infected with a negative control virus. Conversely, use of antisense techniques to reduce levels of Bcl-2 in t(14;18)-containing lymphoma cell lines resulted in enhanced sensitivity to chemotherapeutic drugs. Though all of these chemotherapeutic drugs were still capable of inducing cell cycle arrest in cells containing high amounts of Bcl-2 protein, for some drugs surviving cells with high Bcl-2 were able to re-initiate cell proliferation upon removal of drugs from cultures. Thus, by extending cell survival in the presence of cytotoxic drugs, over-production of the Bcl-2 protein appears to provide cells with an opportunity to repair drug-induced DNA damage and to resume their proliferative activity, as might occur begin cycles of chemotherapy in clinical scenarios. These findings are consistent with clinical correlative studies that have noted an association between alterations in bcl-2 gene structure or expression and poor response to therapy in some groups of patients with lymphoma, leukemia, and prostate cancer. Taken together, these findings strongly argue that the relative level of Bcl-2 protein is an important determinant of the sensitivity of malignant cells to killing by chemotherapeutic

drugs, and suggest that methods to reduce Bcl-2 protein levels or impair Bcl-2 function could markedly improve the efficacy of conventional antineoplastic drugs in the treatment of cancer.

L10 ANSWER 8 OF 43 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
ACCESSION NUMBER: 1999:477872 BIOSIS
DOCUMENT NUMBER: PREV199900477872
TITLE: Cytotoxicity of **taxol** against human **colorectal** cancer cell lines in vitro.
AUTHOR(S): Fang Jin [Reprint author]; Song Jindan [Reprint author]
CORPORATE SOURCE: Department of Cell Biology, College of Basic Medical Sciences, China Medical University, Shenyang, 110001, China
SOURCE: Journal of China Medical University, (Aug., 1999) Vol. 28, No. 4, pp. 241-242. print.
CODEN: ZYDXEN. ISSN: 0258-4646.
DOCUMENT TYPE: Article
LANGUAGE: Chinese
ENTRY DATE: Entered STN: 9 Nov 1999
Last Updated on STN: 9 Nov 1999

AB Objective: Quantitative evaluation of cytotoxicity and sensitivity of **taxol** against human **colorectal** cancer cell lines. Methods: MTT(3-(4,5-dimenthylthiazol-z-yl)-2,5-diphenyl tetrazolium bromide) assay was used to determine the inhibitory action of **taxol** on human **colorectal** cancer cells in vitro, CCL-187 ,CCL-229,CX-1 and Clone A. Results: At maximum physiologically tolerant concentration in plasam (1 X 10-7 mol/L), **taxol** showed inhibitory activity on all four **colorectal** cancer cell lines, when cells were continuously exposed to **taxol** for 72 h. The inhibited growth rate was 34. 54% for CCL-187, 58. 71% for CCL-229, 67. 40% for CX-1, and 70. 87% for Clone A. Taxol showed strong cytotoxicity on CX-1 at IC50 9. 0 X 10-10 mol/L and Clone A at IC50 4. 0 X 10-9 mol/L,which is corresponding to the clinically effective concentration of taxol against several other tumor cells. Conclusion: **Taxol** shown potent effect on human **colorectal** cancer cell lines in vitro, in particular onCX-1 and Clone A lines. The potency increased with the increasing concentration and duration of action for taxol.

L10 ANSWER 6 OF 43 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 1999347914 MEDLINE
DOCUMENT NUMBER: 99347914 PubMed ID: 10421546
TITLE: Paclitaxel sensitivity correlates with p53 status and DNA fragmentation, but not G2/M accumulation.
AUTHOR: Rakovitch E; Mellado W; Hall E J; Pandita T K; Sawant S; Geard C R
CORPORATE SOURCE: Center for Radiological Research, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
CONTRACT NUMBER: CA73061 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, **(1999 Jul 15)** 44 (5) 1119-24.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990729

AB PURPOSE: The antitumor agent paclitaxel (Taxol) has been shown to arrest cells in mitosis through microtubule stabilization and to induce apoptosis. The tumor suppressor gene p53 is implicated in the regulation of cell cycle checkpoints and can mediate apoptotic cell death. Although initial studies demonstrated that various DNA-damaging agents can induce p53, more recent studies have also shown p53 induction following nonDNA-damaging agents, including paclitaxel. We investigated the influence of p53 abrogation on paclitaxel-induced cell kill and correlated the extent of mitotic arrest and DNA fragmentation by paclitaxel with the drug's cytotoxic effect. MATERIALS AND METHODS: The parental human **colorectal** carcinoma cell line (RKO) with wild-type p53 alleles, and two transfected RKO cell lines with inactivated p53 (RKO.p53.13 with transfected mutant p53 and RC 10.3 with HPV-16-derived E6 gene) were exposed to graded doses of **paclitaxel** (1-100 nM) for 24-h intervals. The functional status of p53 in cells was assessed by thymidine and BrdU incorporation following exposure to ionizing radiation (4 Gy). Reproductive integrity following paclitaxel treatment was assessed by clonogenic assay. Immunolabeling and microscopic evaluation were used to assess mitotic accumulation and micronucleation. Apoptosis was assayed using DNA fragmentation analyses. RESULTS: A 4-fold increase in paclitaxel sensitivity was observed among RKO cells deficient in p53 function compared with wild-type RKO cells (IC 50: 4 nM, 1 nM, 1nM for RKO, RKO.p53.13, RC 10.3, respectively). The increased cytotoxic effect in RKO cells with inactive p53 correlated with an increased propensity towards micronucleation and DNA fragmentation following paclitaxel treatment. However, no significant difference in peak mitotic accumulation was observed among RKO cells with functional or abrogated p53. CONCLUSIONS: RKO cells lacking functional p53 demonstrate significantly enhanced sensitivity to paclitaxel compared with that of wild-type RKO cells. This response corresponded with increased micronucleation and DNA fragmentation in cells deficient in p53 function. Although previous published reports of enhanced paclitaxel sensitivity in p53-deficient cells correlated this finding with increased G2/M arrest, we did not observe any significant correlation between paclitaxel-induced cell kill and the degree of mitotic arrest. Our data suggest that apoptosis is the predominant mechanism of paclitaxel cytotoxicity in RKO cells and is likely mediated by a p53-independent process.

L10 ANSWER 24 OF 43 CANCERLIT on STN
ACCESSION NUMBER: 1998082731 CANCERLIT
DOCUMENT NUMBER: 98082731 PubMed ID: 9422268
TITLE: Critical issues in the evolving management of rectal cancer.
AUTHOR: Mohiuddin M; Ahmed M M
CORPORATE SOURCE: A.B. Chandler Medical Center, Department of Radiation Medicine, University of Kentucky, Lexington 40536-0084, USA.
SOURCE: SEMINARS IN ONCOLOGY, **(1997 Dec)** 24 (6) 732-44.
Ref: 105
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 1998082731
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980212
Last Updated on STN: 19980212

AB Evolving trends in the management of rectal cancer have focused on organ preservation, improved quality of life, and survival of patients. A significant shift is underway in our thinking about what constitutes the true rectum and defining the "proximal" and "distal" segments of the rectum. Tumor mobility remains a dominant prognostic factor in patient selection and choice of surgery. A clinical staging with tumor location in the rectum provides a logical algorithm for treatment decision making with either chemoradiation therapy or surgery as initial treatment of choice. Current rectal cancer management has largely focused on postoperative adjuvant radiation strategies with improvement reported for T3 and N+ cases. Recent data from Europe suggests that preoperative radiation has a significant advantage over surgery alone or postoperative treatment. This appears to be borne out by institutional studies of high-dose preoperative radiation (>45 Gy) in the United States. Aggressive preoperative combined chemoradiation has also led to significant downstaging of cancer with pathological complete response rates of 20% to 30%. This offers new options for surgical management of residual disease with endocavitary radiation or local excision. The development of new agents Gemcitabine, **paclitaxel**, and CPT-11 may also prove beneficial. New treatment strategies need to be coordinated with evolving knowledge of the biological behavior of the tumor based on its genetic fingerprints. c-Ki-ras and C-myc mutations have been implicated in tumor initiation and progression. A number of other tumor suppressor genes, APC gene, p53, and DCC have also been implicated in **colorectal** tumor carcigenesis. The modification of biological behavior by mutations in these genes is currently under study. This may guide new treatment strategies significantly reducing the death rates from rectal cancer and improving functional results of treatment.

L10 ANSWER 42 OF 43 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 21
ACCESSION NUMBER: 92:252227 SCISEARCH
THE GENUINE ARTICLE: HN719
TITLE: EFFECTS OF TAXOTERE AND TAXOL ON INVITRO COLONY FORMATION OF FRESHLY EXPLANTED HUMAN TUMOR-CELLS
AUTHOR: HANAUSKE A R; DEGEN D; HILSENBECK S G; BISSERY M C; VONHOFF D D (Reprint)
CORPORATE SOURCE: UNIV TEXAS, HLTH SCI CTR, DEPT MED, DIV ONCOL, DRUG DEV SECT, SAN ANTONIO, TX, 78284; TECH UNIV MUNICH, KLINIKUM RECHTS ISAR, HAMATOL & ONKOL ABT, W-8000 MUNICH 80, GERMANY; CANC THERAPY & RES CTR, SAN ANTONIO, TX, 78240; RHONE POULENC RORER RECH DEV, F-94403 VITRY, FRANCE
COUNTRY OF AUTHOR: USA; GERMANY; FRANCE
SOURCE: ANTI-CANCER DRUGS, (**APR 1992**) Vol. 3, No. 2, pp. 121-124.
ISSN: 0959-4973.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 21

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Taxotere (RP 56976, NSC 628503) is a new semisynthetic analog of **taxol** (NSC 125973) with promising antitumor activity in a variety of preclinical screening systems. Clinical responses after treatment with **taxol** have been observed in ovarian cancer, breast, lung cancer and melanoma. Both agents act through induction of microtubule polymerization. We have studied and compared the antiproliferative action of Taxotere and **taxol** against a variety of freshly explanted human tumor specimens using an in vitro soft agar cloning system. Final concentrations of 0.025-10-mu-g/ml were used for both agents in short-term (1 h) or continuous (14 days) incubations. Taxotere was studied using a 1 h incubation in a total of 167 tumor specimens of which 85 (51%) were evaluable. At 10-mu-g/ml, Taxotere inhibited 32 out of 78 (41%) specimens (colony formation less-than-or-equal-to 0.5 x control). Cytotoxicity of Taxotere was observed against breast, lung, ovarian, **colorectal** cancer and melanoma tumor colony forming units. For comparison, 227 specimens were exposed to **taxol** for 1 h. At 10-mu-g/ml, 32 out of 97 evaluable specimens (33%) were significantly inhibited. Cytotoxicity was observed against breast, lung, ovarian, **colorectal** cancer and melanoma tumor colony forming units. In head-to-head comparisons, 29 specimens were found more sensitive to Taxotere than **taxol**, while only 13 were more sensitive to **taxol** than to Taxotere. These data indicate that cross-resistance between the two agents is incomplete and that on a concentration basis Taxotere is more cytotoxic than **taxol** in the majority of human primary tumor specimens evaluated.

L5 ANSWER 59 OF 87 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:691863 CAPLUS
DOCUMENT NUMBER: 125:316525
TITLE: Single-agent paclitaxel as first-line treatment of metastatic breast cancer: The British experience
AUTHOR(S): Davidson, Neville G.
CORPORATE SOURCE: Department Oncology, North Middlesex Hospital, London, N18 1QX, UK
SOURCE: Seminars in Oncology (**1996**), 23(5, Suppl. 11), 6-10
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacy and safety of paclitaxel (Taxol) was studied as first-line treatment for 30 consecutive patients with metastatic breast cancer. All patients had received adjuvant/neoadjuvant chemotherapy, 22 had prior hormonal therapy, and 26 had received previous adjuvant radiotherapy. Paclitaxel 225 mg/m2 was given as a 3-h infusion without colony-stimulating factor support at 3-wk intervals without excessive dose redn. or delays. The most common nonhematol. toxicities were alopecia (grade 3 in 29 patients) and peripheral neuritis (grade 2 or 3 in 14 patients). The objective response rate was 60% and responses were seen in all disease sites. The median duration of overall response was 30 wk (range, 15 to 75+ weeks) and the estd. median survival time for all patients was 56 wk (range, 1 to 82+ weeks). The response rate and survival times seen with single-agent paclitaxel are encouraging. Future studies must explore paclitaxel in combination with other regimens, with the hope that results will improve further.

L10 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:355845 CAPLUS
DOCUMENT NUMBER: 138:348692
TITLE: Method for treating colorectal carcinoma using a taxane/tocopherol formulation
INVENTOR(S): Palepu, Nagesh; Kessler, Dean; Tustian, Alexander K.; Quay, Steven C.; Constantinides, Panayiotis P.; Lambert, Karel J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Ser. No. 317,499.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 2003087953	A1	20030508	US 2002-188289	20020701	
US 6458373	B1	20021001	US 1998-3173	19980105	
ZA 9800098	A	19980708	ZA 1998-98	19980107	<--
US 6660286	B1	20031209	US 1999-317499	19990524	
US 2003147959	A1	20030807	US 2002-299626	20021119	
US 2003170279	A1	20030911	US 2002-299649	20021119	

PRIORITY APPLN. INFO.:

US 1997-34188P	P	19970107
US 1997-48480P	P	19970603
US 1998-3173	A2	19980105
US 1999-317499	A2	19990524
US 1997-48840P	P	19970606
US 1999-361935	A1	19990727

AB The invention provides methods for administering a taxane compn. for the treatment of cancer. In one aspect, the compns. are not dild. prior to administration. Some embodiments provide methods for administering a taxane as a bolus injection or an i.v. infusion in less than about 30 min. In other aspects, the invention provides methods for administering a taxane to provide high concns. of the taxane in blood or in tumors. Another aspect provides methods for administering a taxane to provide antitumor activities against solid tumors. In some embodiments, the methods provide antitumor activities against tumors that were resistant to conventional taxane administration methods. In some embodiments, the methods provide antitumor activities against colorectal tumors.

L5 ANSWER 65 OF 87 CANCERLIT on STN
ACCESSION NUMBER: 96602925 CANCERLIT
DOCUMENT NUMBER: 96602925
TITLE: Phase I trial of paclitaxel (Taxol) and ifosfamide (IFOS) in previously untreated patients (pts) with non-small cell lung cancer (NSCLC) (Meeting abstract).
AUTHOR: Shepherd F; Latreille J; Eisenhauer E; Fisher B; Hellmann S; Baker M
CORPORATE SOURCE: NCIC Clinical Trials Group, Queen's University, Kingston, Canada.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1995)** 14 A1153.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB **Taxol** has produced **single agent** response rates of 24 and 21% in untreated NSCLC (JNCI 85:384 and 85:388). Ifos is also active in this disease with response rates of 20%. We are performing a phase I trial of ifosfamide 3 g/m2 and Mesna 2.4 g/m2 followed by escalating doses of Taxol (dose levels: 100-225 mg/m2) over 3 hr in previously untreated pts with advanced NSCLC. Cycles are repeated every 3 wk. Cohorts of at least 3 pts are entered at each level. Dose limiting toxicity (DLT) is defined as one or more of the following during the first 2 treatment cycles: gr 4 neutropenia or gr 3 thrombocytopenia greater than or equal to 7d, greater than or equal to gr 3 non-hem toxicity or the need for dose reduction/delay due to toxicity. 25 pts (24 eval) have been accrued at dose levels shown in a chart. There were 13 male and 12 female pts of median age 58 (38-75), median ECOG perf status 1 (0-2), histology: adeno 21, squamous 2, large cell 2; stage III/10 pts, IV/15 pts. Pts at all dose levels are evaluable. The treatment is well tolerated. DLT has been seen in only 2 pts and accrual is continuing to define the maximum tolerated dose for a phase II trial of the combination to assess efficacy.

L12 ANSWER 52 OF 55 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 81239674 MEDLINE
DOCUMENT NUMBER: 81239674 PubMed ID: 6114100
TITLE: Preferential action of a brain detyrosinolating carboxypeptidase on polymerized tubulin.
AUTHOR: Kumar N; Flavin M
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1981 Jul 25)** 256 (14) 7678-86.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198109
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 20000303
Entered Medline: 19810915

AB A carboxypeptidase purified from brain catalyzes the release of COOH-terminal tyrosine without further digesting tubulin. It is distinct from previously described carboxypeptidases, and appears to have specificity for tubulin as it is not inhibited by peptides and proteins with COOH-terminal tyrosine, and because, unlike carboxypeptidase A (which by removing tyrosine from aldolase causes its inactivation), this enzyme does not decrease aldolase activity. The enzyme detyrosinolates both self-assembly-competent (cycle-purified) and -incompetent (phosphocellulose-purified) tubulin. However, under assembly conditions the rate was 2-3-fold higher for competent tubulin. Preincubation of assembly-competent tubulin with podophyllotoxin or colchicine resulted in a parallel concentration-dependent inhibition of tubulin polymerization and detyrosinolation. Similarly, when incompetent tubulin was induced to polymerize by preincubation with purified microtubule-associated protein 2 (an assembly-promoting protein) or **taxol**, the initial rate of its detyrosinolation increased 3-5-fold, and this increase was blocked if podophyllotoxin was also added along with microtubule-associated protein 2 or **taxol** during the preincubation. Oligomers induced by adding vinblastine to incompetent tubulin were also detyrosinolated more rapidly, and the stimulation was abolished by **maytansine**, which has been shown to disperse the vinblastine-induced oligomers. When polymerized and subunit fractions were separated after a steady state mixture had been partially digested with the carboxypeptidase, the former was found to have lost 2-3 times more COOH-terminal tyrosine. Although both polymer and monomer can be detyrosinolated by the enzyme, polymeric and oligomeric forms are the preferred substrates. Carboxypeptidase appeared to release tyrosine at the same rate from populations of short and long microtubules.

L28 ANSWER 39 OF 43 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 20
ACCESSION NUMBER: 92:501113 SCISEARCH
THE GENUINE ARTICLE: JJ837
TITLE: COMBINED ANTIMICROTUBULE ACTIVITY OF ESTRAMUSTINE AND TAXOL IN HUMAN PROSTATIC-CARCINOMA CELL-LINES
AUTHOR: SPEICHER L A (Reprint); BARONE L; TEW K D
CORPORATE SOURCE: FOX CHASE CANC INST, DEPT PHARMACOL, PHILADELPHIA, PA, 19111 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: CANCER RESEARCH, (**15 AUG 1992**) Vol. 52, No. 16, pp. 4433-4440.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Estramustine (EM) and taxol, two antimicrotubule agents with distinct and apparently opposing mechanisms of action, were found to be effective in **combination** in the preclinical **treatment** of EM-resistant and sensitive, wild-type human prostatic carcinoma cell lines. Estramustine **combined** with 1 nM taxol (concentration 100-fold less than that measured in plasma of patients treated with taxol) produced greater than additive effects on the inhibition of cell survival of both wild-type and EM-resistant cells. When **taxol** was used with another **microtubule**-destabilizing drug, vinblastine, no significantly increased cytotoxicity was observed. Other effects on wild-type and EM-resistant cells produced by the **combination** of EM and taxol included (a) an increased proportion of the cells in the S phase of the cell cycle; (b) no mitotic block; and (c) an increase in the percentage of micronucleated cells from a control value of <1% to >20% after drug **treatment**. Immunofluorescent microscopic analysis of the effect of this drug **combination** on the mitotic spindle apparatus revealed specific examples of aberrant mitotic figures, including multiple asters, cells with two distinct spindles, and tripolar spindles able to traverse mitosis and complete cytokinesis. These data provide supportive preclinical evidence for the potential development of an EM/taxol **combination** clinical regimen either for prostate or other cancers.

L12 ANSWER 54 OF 55 CANCERLIT on STN
ACCESSION NUMBER: 79800166 CANCERLIT
DOCUMENT NUMBER: 79800166
TITLE: CYTOLOGIC EVIDENCE THAT **TAXOL**, AN ANTINEOPLASTIC AGENT FROM TAXUS BREVIFOLIA, ACTS AS A MITOTIC SPINDLE POISON.
AUTHOR: Fuchs D A; Johnson R K
CORPORATE SOURCE: Div. Cancer Treatment, NCI, Bethesda, MD, 20014.
SOURCE: Cancer Treat Rep, **(1978)** 62 (8) 1219-1222.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Hierarchical Classification of Proteins
ENTRY MONTH: 197901
ENTRY DATE: Entered STN: 19941107
Last Updated on STN: 19941107

AB The antimitotic and stathmokinetic activity of **taxol**, an antineoplastic agent isolated from Taxus brevifolia which has activity against P388 leukemia and B16 melanoma, were studied in B6D2F1 mice bearing ip P388 leukemia. Beginning 7 days after tumor inoculation when leukemic ascites was evident, **taxol** was injected sc into mice at a dose of 100 mg/kg. At all time points (up to 96 hr postinjection) after this dose, disrupted and abnormal mitotic abnormalities were observed which were similar to those observed following the administration of known mitotic spindle poisons such as vinca alkaloids or **maytansine**. After **taxol** treatment the mitotic index (MI) progressively increased from a control value of 1-2% to a value of 8% at 12 hr. The MI returned to control levels 14 hr after drug administration. **Taxol** was much less efficient than other mitotic spindle poisons in producing mitotic arrest. Investigations on the binding of **taxol** to tubulin may provide more insight into its antitumor activity. (9 Refs)

L9 ANSWER 54 OF 57 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 89066916 MEDLINE
DOCUMENT NUMBER: 89066916 PubMed ID: 3198696
TITLE: Estramustine binds MAP-2 to inhibit microtubule assembly in vitro.
AUTHOR: Stearns M E; Tew K D
CORPORATE SOURCE: Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, PA 19111.
CONTRACT NUMBER: CA06927 (NCI)
CA43783-01 (NCI)
SOURCE: JOURNAL OF CELL SCIENCE, (1988 Mar) 89 (Pt 3) 331-42.
Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19890126

AB We have investigated the ability of estramustine to bind to rat brain microtubule-associated proteins (MAPs) and purified MAP-2 in vitro. [3H]estramustine's relative affinity for tubulin and MAPs was assessed by gel filtration chromatography, immunoprecipitation and binding assays. Scatchard analysis demonstrated a specific affinity of the drug for MAP-2. Calculations from kinetic parameters and non-linear regression analysis gave a Kd of 15 microM, and a Bmax of 3.4 x 10(-7)M ml-1. Extrapolation of this value suggested that each MAP-2 molecule binds approximately 20 molecules of estramustine. **Microtubule** assembly studies and SDS-polyacrylamide gel electrophoresis revealed that at 20-60 microM levels, **estramustine** inhibited the association of MAPs with **taxol microtubules**. Turbidity (A350) studies further demonstrated that 20-60 microM-estramustine inhibited MAP-2-driven tubulin assembly and produced microtubule disassembly. Electron-microscopic studies confirmed the centrifugation and turbidity results. The data demonstrated that estramustine can bind MAPs and MAP-2 specifically, thereby inhibiting microtubule assembly.

L9 ANSWER 54 OF 57 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 89066916 MEDLINE
DOCUMENT NUMBER: 89066916 PubMed ID: 3198696
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AUTHOR: Stearns M E; Tew K D
CORPORATE SOURCE: Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, PA 19111.
CONTRACT NUMBER: CA06927 (NCI)
CA43783-01 (NCI)
SOURCE: JOURNAL OF CELL SCIENCE, (1988 Mar) 89 (Pt 3) 331-42.
Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19890126

AB We have investigated the ability of estramustine to bind to rat brain microtubule-associated proteins (MAPs) and purified MAP-2 in vitro. [3H]estramustine's relative affinity for tubulin and MAPs was assessed by gel filtration chromatography, immunoprecipitation and binding assays. Scatchard analysis demonstrated a specific affinity of the drug for MAP-2. Calculations from kinetic parameters and non-linear regression analysis gave a Kd of 15 microM, and a Bmax of 3.4 x 10(-7)M ml-1. Extrapolation of this value suggested that each MAP-2 molecule binds approximately 20 molecules of estramustine. **Microtubule** assembly studies and SDS-polyacrylamide gel electrophoresis revealed that at 20-60 microM levels, **estramustine** inhibited the association of MAPs with **taxol microtubules**. Turbidity (A350) studies further demonstrated that 20-60 microM-estramustine inhibited MAP-2-driven tubulin assembly and produced microtubule disassembly. Electron-microscopic studies confirmed the centrifugation and turbidity results. The data demonstrated that estramustine can bind MAPs and MAP-2 specifically, thereby inhibiting microtubule assembly.

L10 ANSWER 35 OF 43 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:3018 CAPLUS
DOCUMENT NUMBER: 124:105827
TITLE: The activity of paclitaxel in gastrointestinal tumors
AUTHOR(S): Ajani, Jaffer A.; Ilson, David H.; Kelsen, David P.
CORPORATE SOURCE: M.D. Anderson Cancer Center, University Texas, Houston, TX, 77030-4095, USA
SOURCE: Seminars in Oncology (**1995**), 22(5, Suppl. 12), 46-50
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gastrointestinal malignancies, which are common around the world, are relatively refractory to available cancer chemotherapeutic agents, necessitating a search for new agents able to improve palliation and survival of patients with advanced disease. Currently, metastatic or local-regional unresectable carcinoma of the esophagus or gastroesophageal junction carries a dismal prognosis. Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), a new mitotic spindle inhibitor, has been studied in patients with advanced gastrointestinal carcinoma. In this phase II National Cancer Institute-sponsored study, previously untreated patients with unresectable local-regional or metastatic carcinoma of the esophagus or gastroesophageal junction (either squamous cell carcinoma or adenocarcinoma) received a starting dose of paclitaxel of 250 mg/m2 administered by a 24-h i.v. infusion (with premedication) repeated every 21 days; all patients received s.c. granulocyte colony-stimulating factor 5 .mu.g/kg daily 24 h after the completion of the paclitaxel infusion. Fifty-one of 53 patients were assessable for response and response duration. Thirty-three patients had adenocarcinoma and 18 had squamous cell carcinoma. Sixteen (31%) patients achieved a response (one complete and 15 partial) and 11 (22%) achieved a minor response. Among 33 patients with adenocarcinoma, 12 (36%; 95% confidence interval, 14% to 58%) achieved either a complete (one patient) or partial (11 patients) response and six patients (18%) had a minor response. Four (22%; 95% confidence interval, 3% to 41%) of 18 patients with squamous cell carcinoma had a partial response and four (22%) had a minor response. At a median follow-up of 12+ months, 28 patients remain alive with an actuarial median survival duration of 10.2 mo (range, 2 to 20+ months). These data suggest that paclitaxel is active against adenocarcinoma as well as squamous cell carcinoma of the esophagus. In a subsequent study, the combination of paclitaxel (175 mg/m2 over 3 h on day I), cisplatin (20 mg/m2 on days 1 to 5), and 5-fluorouracil (1,000 mg/m2/d in the first 10 patients but then reduced to 750 mg/m2/d, given as a continuous infusion on days 1 to 5) repeated every 28 days was given to patients with advanced adenocarcinoma or squamous cell carcinoma of the esophagus. Of 46 patients accrued (target accrual, 60), 35 are men and 11 are women, 30 have adenocarcinoma and 16 have squamous cell carcinoma. Among 39 patients evaluated for response so far, one has had a complete response and 16 have had partial responses (overall response rate, 44%; 95% confidence interval, 28% to 59%). Five patients have had a minor response. The median granulocyte nadir was 1,200/.mu.L. Seven patients have been hospitalized to manage fever assocd. with neutropenia. With the reduced starting dose of 5-fluorouracil, tolerance has improved substantially both in the inpatient and outpatient settings, resulting in a low frequency of grade 3 or 4 nonhematol. toxicity. Preliminary data suggest that this is an active combination against squamous cell carcinoma and adenocarcinoma of the esophagus. A phase III study may be warranted to define the contribution of paclitaxel. Thus far, **paclitaxel** has demonstrated limited or no activity in trials conducted in patients with pancreatic, **colorectal**, or gastric carcinoma. Clin. investigation continues

to further explore the activity of paclitaxel in gastrointestinal malignancies.

L6 ANSWER 9 OF 10 CANCERLIT on STN
ACCESSION NUMBER: 97618990 CANCERLIT
DOCUMENT NUMBER: 97618990
TITLE: Cure of human small cell lung cancer xenografts in SCID mice by a hN901-maytansinoid immunoconjugate (Meeting abstract).
AUTHOR: Liu C; Bourret L A; Derr S M; Widdison W C; Lambert J M; Blattler W A; Chari R V
CORPORATE SOURCE: lmmunoGen Inc, Cambridge, MA 02139.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)** 38 A190.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Changing the in vivo distribution of cytotoxic agents through conjugating to tumor-associated monoclonal antibodies may allow the introduction of novel more potent agents for the treatment of cancer which hold the promise of increased anticancer efficacy.The maytansinoid drug DM1 is in vitro a more potent cytotoxic agent by 100- to 1000-fold than anticancer drugs currently in clinical use. We have previously shown that conjugation of DM1 to monoclonal antibodies renders it a highly efficacious agent against cancers of breast and colon. Here we demonstrate its effectiveness on small cell lung cancers (SCLC) when conjugated to **hN901** a humanized monoclonal **antibody** that targets **CD56** which is expressed on all SCLC. The immunoconjugate hN901-DM1 was evaluated for antitumor activity and specificity in vitro and in vivo against the human SCLC cell lines SW2 and N417. hN901-DM1 showed high antigen-specific cytotoxicity for the cultured SCLC cells(IC50 = 6 x 10(-11) M). In vivo iv administration of hN901-DM1 at a conjugated DM1 dose of 300 ug/kg/d x 5 cured all mice bearing subcutaneous SCLC xenografts while the currently used drugs for SCLC cisplatin and etoposide either used as single agents or in combination at their maximum tolerated doses only moderately delayed the tumor growth. The preclinical results indicate that hN901-DM1 is a promising agent that may be worthy of clinical evaluation.

L25 ANSWER 51 OF 70 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 28
ACCESSION NUMBER: 94:109053 SCISEARCH
THE GENUINE ARTICLE: MW572
TITLE: TAXOL (PACLITAXEL) - A NOVEL ANTI-MICROTUBULE AGENT WITH REMARKABLE ANTINEOPLASTIC ACTIVITY
AUTHOR: FOA R (Reprint); NORTON L; SEIDMAN A D
CORPORATE SOURCE: DIPARTIMENTO SCI BIOMED & ONCOL UMANA, SEZ CLIN, VIA GENOVA 3, I-10126 TURIN, ITALY (Reprint); MEM SLOAN KETTERING CANC CTR, DEPT MED, DIV SOLID TUMOR ONCOL, BREAST & GYNECOL CANC MED SERV, NEW YORK, NY, 10021
COUNTRY OF AUTHOR: ITALY; USA
SOURCE: INTERNATIONAL JOURNAL OF CLINICAL & LABORATORY RESEARCH, (**JAN 1994**) Vol. 24, No. 1, pp. 6-14.
ISSN: 0940-5437.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 62

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Taxol** (**paclitaxel**), an anti-**microtubule** agent extracted from the needles and bark of the Pacific yew tree Taxus brevifolia, has shown a remarkable anti-neoplastic effect in human cancer in phase I studies and early phase II and III trials thus far conducted. This has been reported primarily in advanced ovarian and breast cancer, although significant activity has also been documented in small-cell and non-small-cell lung cancer, head and neck cancers, and with lower activity in metastatic melanoma. The clinical utilization of Taxol had been previously somewhat restricted by its limited availability, a limitation that has recently been overcome by **combined** efforts of pharmaceutical, agricultural, and governmental agencies. In this review we shall address the pre-clinical data which have led to the use of Taxol in man, the main clinical results thus far obtained, the toxicities associated with its use, current ongoing trials and future clinical directions of this promising agent.

L25 ANSWER 25 OF 70 CANCERLIT on STN
ACCESSION NUMBER: 97149779 CANCERLIT
DOCUMENT NUMBER: 97149779 PubMed ID: 8996573
TITLE: A phase I study of etoposide phosphate plus paclitaxel.
AUTHOR: Brooks D J; Alberts D S
CORPORATE SOURCE: Arizona Cancer Center, University of Arizona Health Sciences Center, Tucson, USA.
SOURCE: SEMINARS IN ONCOLOGY, **(1996 Dec)** 23 (6 Suppl 13) 30-3.
Journal code: 0420432. ISSN: 0093-7754.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 97149779
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305

AB Etoposide phosphate (Etopophos; Bristol-Myers Squibb Company, Princeton, NJ) is a water-soluble derivative of etoposide, a semisynthetic podophyllotoxin that is important in the treatment of a variety of malignancies, including lung cancer, germ cell tumors, non-Hodgkin's lymphoma, Hodgkin's lymphoma, acute leukemia, etc. Because etoposide is poorly water soluble, it must be dissolved in a polysorbate 80-based solvent mixture, which is moderately allergenic and requires a large volume of saline for administration. Etoposide phosphate is water soluble and is rapidly converted in vivo to etoposide by endogenous phosphatases. Because it is water soluble, etoposide phosphate can be administered in volumes much smaller than those required with etoposide therapy, permitting rapid intravenous administration in the outpatient setting. We recently reported the results of a phase I study using etoposide phosphate on a bolus, daily x 5 schedule. Like others, we demonstrated that etoposide phosphate has pharmacokinetic properties virtually identical to those of etoposide. Our dose-finding study indicated that etoposide phosphate can be used in doses up to 100 mg/m2/d x 5 every 3 weeks in patients who have not had extensive prior chemotherapy, and that a dose of 75 mg/m2 would be appropriate for patients who had undergone multiple prior therapies or who had prior radiotherapy. The dose-limiting toxicity was neutropenia. **Paclitaxel**, a **microtubule**-stabilizing agent, is active against a variety of solid and hematopoietic malignancies that overlap with those against which etoposide is active. Because the mechanisms of action of these two agents differ, it is logical to suppose that the **combination** of the two agents might produce some additive effect when used to treat cancers that respond to both individual agents. We therefore undertook a phase I study using paclitaxel as a 3-hour infusion in **combination** with a 5-minute infusion of etoposide phosphate daily x 3 every 21 days. We used the 3-hour paclitaxel schedule because it has been shown to be less myelotoxic than longer infusions at the same doses. Our goal in this ongoing study is to determine the maximum tolerated doses of the two drugs in **combination**, to determine the toxicities of the regimen, and to assess its anticancer activity.